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EXAMINER	
LAM, ANN Y	
ART UNIT	**PAPER NUMBER**
1641	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/835,298	DAHLEN ET AL.	
	Examiner	Art Unit	
	Ann Y. Lam	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-28,32-34 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-28,32-34 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 April 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/30/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 29-31 and 35-37 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 1-22 are canceled.

Claims 23-28, 32-34 and 38 are examined below.

35 USC § 112, 6th Paragraph

The Office notes that the language "means for determining cardiac mortality rate" in claim 23, line 9, and claim 25, line 10, respectively, and "means for determining binding" in claim 23, line 8, and claim 25, line 8, respectively, are being treated under *35 USC § 112, 6th Paragraph.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23-28, 32-34 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Jackowski**, [5,290,678], in view of **Antman et al.**, ["Cardiac-specific

Troponin I Levels to Predict the Risk of Mortality in Patients with Acute Coronary Syndromes", The New England Journal of Medicine, (1996), pp. 1342-1349, Vol. 335, No. 18], and further in view of **Richards et al.**, ["Neuroendocrine prediction of left ventricular function and heart failure after acute myocardial infarction", Heart, (1999); 81: 114-120].

Jackowski teaches the invention substantially as claimed. Jackowski teaches a multimarker approach comprising the use of antibodies for detecting the presence of at least three markers of cardiac damage in a patient's serum and that the combined responses of reagents indicates the diagnostic condition of the patient (col. 5, lines 17-21, and lines 43-51).

Jackowski teaches that troponin may be one of the markers that may be detected for this purpose (col. 8, lines 28-29). However, Jackowski does not teach detecting the combination of troponin and BNP, nor for the purpose of detecting cardiac mortality.

Antman et al. however teach that cardiac troponin I can be measured by immunoassay using antibodies that recognize cardiac troponin I (see page 1343, left column, last paragraph.) Moreover, Antman et al. teach that cardiac troponin I in blood is an independent risk factor that identifies patients presenting with unstable angina or non-Q-wave myocardial infarction who are at increased risk of death (see page 1347, left col., last paragraph.) Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the multimarker assay taught by Jackowski using cardiac troponin I to predict increased risk of death because Antman et al. teach that cardiac troponin I in blood is an independent risk factor that identifies

patients presenting with unstable angina or non-Q-wave myocardial infarction who are at increased risk of death. One of ordinary skill in the art would recognize the medical benefits of detecting increased risk of death.

Moreover, Richards et al. teach that plasma BNP measured within 1 to 4 days of acute myocardial infarction is a powerful independent predictor of death over the subsequent 14 months (see page 114, left column, last paragraph under the heading "*Conclusions*"). Richards et al. collected blood samples from patients (see page 114, right col., last paragraph) and tested for cardiac peptides using an immunoassay (i.e., a binding assay using antibodies), (see page 115, left col., 1st paragraph). The patients in the study had acute myocardial infarction (see table 3 on page 117). Moreover, Richards et al. teach that adding BNP in a multivariate analyses added additional information in predicting the composite end point of death (see page 118, right column, last paragraph). Richards et al. concluded that stratification of patients into low and high risk groups can be greatly facilitated by plasma BNP measurements and that these could be included in the routine clinical work up of patients following myocardial infarction (see page 119, right column, last paragraph, under the heading "CONCLUSION"). While Richards et al. do not specifically state that the same type of analysis, i.e., radioimmunoassay, as used in the experiment may be performed for clinical analyses, it is understood to be the same type, i.e., immunoassay (which uses antibodies). (Alternatively, it would have been obvious to one of ordinary skill in the art that the same type of assay, i.e., immunoassay, used by Richards et al. in the

experiment may be used for clinical analyses because Richards et al. teach that BNP can be detected using immunoassays.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to provide BNP as taught by Richards et al. as a marker in the multimarker assay taught by Jackowski modified by Antman et al. for the purpose of predicting cardiac mortality rate in patients with acute myocardial infarction because Richards et al. teach that BNP is a powerful predictor of death in patients with acute myocardial infarction (see page 114, left column, last paragraph under the heading "*Conclusions*") and that adding BNP as a marker to a multivariate analyses added additional information in predicting death (see page 118, right col., last paragraph).

To elaborate on the suggestions and motivations to combine the references, it is noted that Jackowski teaches a method of detecting more than one marker of cardiac damage (see col. 5, lines 18-20), the combined responses indicating the diagnostic condition of a patient (col. 5, lines 50-52). The basis for this multiple marker (or multimarker) approach is in part due to the fact that different markers of cardiac damage are released at different times (see for example, column 2, lines 58-63 and column 7, lines 47-50, disclosing that levels of CK-MB are not elevated until 6-8 hours after the onset of myocardial infarction and do not peak until after 12 hours and therefore its detection is not of use alone as a diagnostic test.) The basis for the multiple marker approach is also based on the usefulness of detecting multiple markers for determining different medical conditions related to cardiac damage (col. 5, lines 27-29, and col. 7, lines 47-67.) The invention of Jackowski thus utilizes different combinations of

antibodies such that different cardiac markers are assessed, including markers that ensure detection of cardiac tissue damage at an early stage of patient chest pain (col. 8, lines 16-20), and markers that can detect myocardial infarction many after onset of chest pain where the patient is in the later stages of myocardial infarction (col. 8, line 34-38) for the purpose of detecting myocardial infarction or unstable angina (col. 7, lines 52-66.) In short, Jackowski teaches the basis for a multiple marker approach in detecting markers of cardiac damage. While Jackowski discloses specific cardiac markers but does not disclose BNP, and teaches use of the markers for the purpose of detecting myocardial infarction or unstable angina (col. 7, lines 52-66), rather than for predicting cardiac mortality rate, one of ordinary skill in the art would nevertheless recognize that Jackowski teaches the general concept of a multiple marker approach for determining different medical conditions related to cardiac damage particularly where the markers are released and peak at different times. Moreover, Antman et al. and Richards et al. teach, respectively, that cardiac troponin I and BNP are predictors of death in patients with myocardial infarction (see Antman et al. page 1347, bottom of left column; and Richards et al., page 114, bottom of left column). While Jackowski does not teach a method of predicting increased risk of death, one of ordinary skill in the art would recognize the medical benefits of detecting increased risk of death taught by Antman et al. and Richards et al. Moreover, one of ordinary skill in the art would recognize the benefit of measuring troponin I as taught by Antman et al. and BNP as taught by Richards et al. in a multiple marker approach generally taught by Jackowski because Jackowski suggests that different cardiac markers are detectable and peak at

different times after cardiac injury and Antman et al. and Richards et al. disclose different time frames for measuring troponin I and BNP for predicting death, with Antman et al. emphasizing that troponin I permits early identification of patients at increased risk of death, even where measured 6 hours or less after the onset of chest pain, and especially above 6 hours to 24 hours, and Richards et al. disclosing that BNP is powerful predictor of death 1-4 days after the onset of acute myocardial infarction. Furthermore, one of ordinary skill in the art would be suggested to measure troponin I as an early predictor of death, as taught by Antman et al., and BNP as a powerful predictor of death, particularly because Richards et al. teach that measuring the level of BNP could reasonably be included in the routine clinical work up of patients following myocardial infarction, thus suggesting that measuring BNP levels should be coupled with other clinical procedures performed on patients with myocardial infarction. Thus, the disclosures of Antman et al. and Richards et al. provide motivations and suggestions for detecting troponin I and BNP in a multiple marker approach taught by Jackowski, either as additional markers to those disclosed by Jackowski, i.e., for the additional determination of a medical condition, specifically predicting likelihood of death, or as a separate multiple marker assay method for the purpose of predicting likelihood of death. One of ordinary skill in the art would recognize from the disclosure by Antman et al. and Richards et al. that detecting both troponin I and BNP provide the advantage of a better prediction of likelihood of death as these cardiac markers as disclosed as being detectable at different times, and based on the Jackowski disclosure

that a multiple marker approach provides more information and thus a better determination of a medical condition of a patient.

Thus, with respect to independent claims 23, 25, 27 and 33, Richards et al. teach the steps of contacting a sample with a second antibody (i.e., antibodies used in the radioimmunoassay on page 115, left col., 1st paragraph) that specifically binds to a second marker (BNP), (see page 118, right column, 1st full paragraph);

providing means for determining binding between each of said respective markers and each of said respective antibodies (i.e. the radioimmunoassay, page 115, left col., first paragraph),

whereby said binding provides a means for determining cardiac mortality rate (page 118, right col., last paragraph). (As to claims 27 and 33, the prognosis is considered to be cardiac mortality rate, or death.)

As to the following claims, the references teach the limitations as follows.

As to claims 24, 26, 28,and 34, said body fluid is blood (Antman et al., page 1343, left col., 3rd full paragraph; and Richards et al., page 114, right col., last paragraph).

Regarding the preamble in claims 23 and 27, the above method of predicting cardiac mortality rate is performed on a patient that *has* an acute coronary syndrome (see Antman et al., page 1347, left col., last paragraph; and see Richards et al. page 114, left column, last paragraph).

With respect to 32 and 38, the prognosis is considered to be mortality rate or subsequent death (see Antman et al., page 1347, left col., last paragraph; and see Richards et al. page 114, left column, last paragraph.)

Regarding the preamble in claims 25 and 33, while the references teach that the markers may be performed on patients *with* acute coronary syndromes, such as acute myocardial infarction (see above with respect to claims 23 and 27), the references however do not specifically state that the patients were actually *diagnosed* with acute coronary syndromes. However, the references suggest that a method of predicting mortality rate using the markers should be performed on those patients who have been diagnosed with acute coronary syndromes because they suggest the benefits of performing such a method on high risk groups (which would include those that actually have been diagnosed with acute coronary syndrome). For example, Antman et al. teach that the disclosed method of predicting mortality permits the early identification of patients at increased risk of death (page 1348, right column, last paragraph). Moreover, Richards et al. suggest that stratification of patients into low and high risk groups can be greatly facilitated by plasma BNP measurements and that these could be included in the routine clinical work up of patients following myocardial infarction (see page 119, right column, last paragraph).

Response to Remarks

Applicant's arguments and affidavit filed October 30, 2006 have been fully considered.

As to Applicants' argument concerning the 112, second paragraph rejection, the rejection of the claims as being indefinite is hereby withdrawn for the following reasons. Applicants assert on page 5 that the rejected claims refer to a method for assigning a prognosis (e.g., a likelihood of death) to a patient. Applicants also assert on page 7 that rather than being indicative of indefiniteness, Examiner's allegations and the questions posed by Examiner relate to the breadth of the claims. Applicants further assert that the claims embrace different ways in which the immunoassay results may be used to assign a mortality rate and also that the precise methods to be used are best left to the discretion of the skilled artisan, depending for example upon the level of sensitivity and specificity desired from the method. Based on Applicants' assertion, the claims are thus interpreted as broadly as Applicants' have argued. That is, based on Applicants' assertion, the claims are interpreted as broadly as to encompass a method wherein determining that a level is at least above the level measured in a normal population of either marker of the two groups of markers listed by Applicants, indicate an increased likelihood of death. It is also noted that based on Applicants' assertions indicated above, the term cardiac mortality rate is broadly interpreted to mean likelihood of death, and the term prognosis encompasses predicting likelihood of death. In summary, Applicants' arguments appear to indicate that the claims encompass such broad interpretations as

mentioned above, and thus such broad interpretations are given to the claims and the rejections under 112, second paragraph are hereby withdrawn.

Applicants' arguments and affidavit concerning the 103 rejection however are not persuasive for the following reasons.

The following is a summary of Applicants' arguments, to which Examiner will respond further below.

Applicants argue on page 8 of the response that a clear flaw in Examiner's understanding of the claimed invention is readily apparent from the initial analysis offered by Examiner, which states that "Jackowski teaches the invention substantially as claimed". Applicants assert that Examiner's acknowledgement that Jackowski does not teach detecting the combination of troponin and BNP, nor for the purpose of detecting cardiac mortality, makes the assertion that "Jackowski teaches the invention substantially as claimed" all the more curious.

Applicants point out that the alleged motivation offered for combing the teachings of Antman et al. and Richards et al. is that Richards et al. teach that BNP is a powerful predictor of death in patients with acute myocardial infarction...and that adding BNP as a marker to a multivariate analyses added additional information in predicting death. Applicants assert that to the extent that Examiner's reasoning, which is based on a partial quote of a sentence from Richards et al. on page 118, right column, last paragraph, implies that the cited art indicates BNP measurements added additional information to cardiac troponin measurements, the reasoning is incorrect. Applicants assert that the cited section of Richards et al. states that BNP measurements "added

additional information beyond clinical features, noradrenaline concentrations, and LVEF (left ventricular ejection fraction) in predicting heart failure or the composite end point of death and/or heart failure." Applicants argue that nothing in Richards et al. mentions or even contemplates combining BNP measurements with cardiac troponin measurements much less indicates that the two measurements might add "additional information" to one another.

Applicants further state that that the rejection may be best viewed as an assertion that combining BNP measurements with cardiac troponin measurements would be prima facie obvious, as the prior art allegedly teaches that each marker individually is useful for the same purpose, specifically, prediction of death in patients with acute myocardial infarction. Applicants argue that no publication of record discloses or suggests to combine BNP and cardiac troponin measurements for assigning prognosis in ACS patients. Applicants further note that Patent 6,461,828, which was the subject of an interference with the present patent application includes a list in Table 1 of literally thousands of possible markers supposedly related to cardiac injury. Applicants argue that Examiner's selection of BNP and cardiac troponin measurements from amongst thousands of possible choices, to arrive at a method for assigning prognosis in ACS patients can only be made improperly based on hindsight using Applicants' disclosure or the use of an "obvious to try" rationale. Applicants assert that there must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from Applicants' disclosure.

Applicants' arguments are not persuasive in view of the teachings of the prior art, which will be elaborated as follows.

Jackowski teaches a method of detecting more than one marker of cardiac damage (see col. 5, lines 18-20), the combined responses indicating the diagnostic condition of a patient (col. 5, lines 50-52). It is emphasized that the basis for this multiple marker (or multimarker) approach is in part due to the fact that different markers of cardiac damage are released at different times (see for example, column 2, lines 58-63 and column 7, lines 47-50, disclosing that levels of CK-MB are not elevated until 6-8 hours after the onset of myocardial infarction and do not peak until after 12 hours and therefore its detection is not of use alone as a diagnostic test.) he basis for the multiple marker approach is also based on the usefulness of detecting multiple markers for determining different medical conditions related to cardiac damage (col. 5, lines 27-29, and col. 7, lines 47-67.) The invention of Jackowski thus utilizes different combinations of antibodies such that different cardiac markers are assessed, including markers that ensure detection of cardiac tissue damage at an early stage of patient chest pain (col. 8, lines 16-20), and markers that can detect myocardial infarction many after onset of chest pain where the patient is in the later stages of myocardial infarction (col. 8, line 34-38) for the purpose of detecting myocardial infarction or unstable angina (col. 7, lines 52-66.) In short, Jackowski teaches the basis for a multiple marker approach in detecting markers of cardiac damage. However, as noted in the Office action, Jackowski does not teach predicting cardiac mortality using troponin I or BNP,

nor does Jackowski teach BNP as a marker. These teachings however are taught by the secondary references, as discussed further below.

First, it is emphasized that while Jackowski discloses specific cardiac markers but does not disclose BNP, and teaches use of the markers for the purpose of detecting myocardial infarction or unstable angina (col. 7, lines 52-66), rather than for predicting cardiac mortality rate, one of ordinary skill in the art would nevertheless recognize that Jackowski teaches the general concept of a multiple marker approach for determining different medical conditions related to cardiac damage particularly where the markers are released and peak at different times. Moreover, Antman et al. and Richards et al. teach, respectively, that cardiac troponin I and BNP are predictors of death in patients with myocardial infarction (see Antman et al. page 1347, bottom of left column; and Richards et al., page 114, bottom of left column).

Antman et al. teach that cardiac troponin I is an independent risk factor that identifies patients presenting with unstable angina or non-Q-wave myocardial infarction who are at increased risk of death (page 1345 lower right column; and page 1347, bottom of left column.) Antman et al. also disclose in figure 2 that the measurement of troponin I taken from as early as 0 to 6 hours after onset of chest pain show an increase in risk of mortality where the cardiac troponin I level is at least 0.4 ng/milliliter and that the prognostic value of cardiac troponin I was greatest during the time period greater than 6 to 24 hours after chest pain as compared to 0 to 6 hours and 0 to 24 hours (see figure 2 and also page 1348, second full paragraph.) Antman et al. also pointed out that previous studies of troponin T used blood specimens obtained serially 24 to 48 hours

after presentation in order to screen for elevated levels of that serum cardiac marker but that the study performed by Antman et al. used a single measurement of troponin I at presentation (see page 1348, third full paragraph.) It is also noted that Antman et al. teach that cardiac troponin I permits the *early* identification of patients at increased risk of death (page 1348, right column.)

Moreover, Richards et al. teach that plasma BNP measured 1 to 4 days of acute myocardial infarction is a powerful independent predictor of death over the subsequent 14 months (see page 114, left column, under *"Conclusion"*.). It is emphasized that Richards et al. teach that the level of BNP was predictive of death where BNP measurement was 1 to 4 days (see page 114, left column, under *"Design"* and also table 3). While Richards et al. indicate that the level of BNP added additional information beyond clinical features, noradrenaline concentrations, and LVEF in predicting the composite end point of death (see page 118, right column, last paragraph), rather than in addition to the level of, for example, Troponin I, one of ordinary skill in the art, based on the teachings of Jackowski as well as Antman et al. and Richards et al., would recognize the benefit of a multiple marker approach to predicting death using Troponin I as taught by Antman et al. and BNP as taught by Richards et al., as Antman et al. and Richards et al. disclose different time frames for measuring troponin I and BNP for predicting death.

Suggestions or motivations for one of ordinary skill in the art to combine the references are found in each of the cited references. While Jackowski does not teach a method of predicting increased risk of death, one of ordinary skill in the art would

recognize the medical benefits of detecting increased risk of death taught by Antman et al. and Richards et al. Moreover, based on the teachings of Jackowski that markers of cardiac damage may be released and peak at different times as well as the disclosure of Antman et al. that the level of cardiac troponin I above a certain level shows an increase in mortality even as early as 0 to 6 hours and that the prognostic value of cardiac troponin I was greatest during the time period greater than 6 to 24 hours after chest pain as compared to 0 to 6 hours and 0 to 24 hours (see figure 2 and also page 1348, second full paragraph), as well as the disclosure of Richards et al. that the level of BNP was predictive of death where BNP measurement was 1 to 4 days (see *"Conclusions"* on page 114 and also table 3), one of ordinary skill in the art would recognize the benefit of detecting both troponin I and BNP to predict mortality rate in a multiple marker approach taught by Jackowski because Antman et al. and Richards et al. disclose different time frames for measuring troponin I and BNP for predicting death. It is emphasized that Antman et al. disclose that troponin I permits the early identification of patients at increased risk of death (page 1348, right column; and also left column, third full paragraph) and that levels of troponin I is predictive of death even from 0 to 6 hours, and a stronger correlation is made if the measurement of the elevated levels of troponins is made 6 to 24 hours after onset of chest pain (see figure 2). Furthermore, it is emphasized that Richards et al. disclose that BNP is a powerful predictor of death where it is measured within 1-4 days (see *"Conclusions"* on page 114). It is emphasized that the measurements of BNP were made 1-4 days, or 24 to 96 hours, after myocardial infarction (see abstract on page 114, under the heading

"Design", and also on page 114, right column, last partial paragraph.) Thus, one of ordinary skill in the art would recognize the benefit of detecting the level of both troponin I and BNP as predictors of death because these markers are disclosed to be predictors of death at different times, troponin I, as early as 0 to 6 hours, and especially 6 to 24 hours after onset of chest pain, as taught by Antman et al., and BNP from 1 to 4 days after acute myocardial infarction, as taught by Richards et al.

Moreover, it is emphasized that Richards et al. also suggest measuring the level of BNP in addition to other routine clinical work up of a patient following myocardial infarction (page 119, right column, last paragraph). While it is not clear that "routine clinical work" includes measuring other markers of cardiac damage, Richards et al. nevertheless suggest measuring BNP levels as an additional test because it is a powerful predictor of death in patients with acute myocardial infarction.

Thus, the disclosures of Antman et al. and Richards et al. provide motivations and suggestions for detecting troponin I and BNP in a multiple marker approach taught by Jackowski, either as additional markers to those disclosed by Jackowski, i.e., for the additional determination of a medical condition, specifically predicting likelihood of death, or as a separate multiple marker assay method for the purpose of predicting likelihood of death. One of ordinary skill in the art would recognize from the disclosure by Antman et al. and Richards et al. that detecting both troponin I and BNP provide the advantage of a better prediction of likelihood of death as these cardiac markers as disclosed as being detectable at different times, and based on the Jackowski disclosure

that a multiple marker approach provides more information and thus a better determination of a medical condition of a patient.

Thus, contrary to Applicants' assertion, Examiner's selection of BNP and cardiac troponin measurements from amongst many possible choices, to arrive at a method for assigning prognosis in ACS patients is not improperly based on hindsight using Applicants' disclosure or the use of an "obvious to try" rationale. Specifically with respect to Applicants' mentioning of the thousands of possible markers in Patent 6,461,828, and that Examiner's selection of BNP and cardiac troponin for combination is improperly based on hindsight or an "obvious to try" rationale, Examiner's selection of BNP and cardiac troponin is not based on Patent 6,461,828, but rather is based on the teachings of the cite prior art (Jackowski, Antman et al. and Richards et al), which provide the reasons or suggestions for selecting the markers. In short, one of ordinary skill in the art would recognize the benefit of measuring troponin I as taught by Antman et al. and BNP as taught by Richards et al. in a multiple marker approach generally taught by Jackowski because Jackowski suggests that different cardiac markers are detectable and peak at different times after cardiac injury and the disclosures of Antman et al. and Richards et al. suggest that troponin I and BNP can be detected at different times as a predictor of death, with Antman et al. emphasizing that troponin I permits early identification of patients at increased risk of death, even where measured 6 hours or less after the onset of chest pain, and especially above 6 hours to 24 hours, and Richards et al. disclosing that BNP is powerful predictor of death even 4 days after the onset of acute myocardial infarction. Moreover, one of ordinary skill in the art would also

be suggested to measure troponin I as an early predictor of death, as taught by Antman et al., and BNP as a powerful predictor of death, particularly because Richards et al. teach that measuring the level of BNP could reasonably be included in the routine clinical work up of patients following myocardial infarction, thus suggesting that measuring BNP levels should be coupled with other clinical procedures performed on patients with myocardial infarction.

Applicants also argue on page 11 of the response that even assuming that a prima facie case has been stated, such would be rebutted by a showing of unexpected results and acclimation (tributes paid to and adoption of the invention by others).

Applicants argue that it was unexpected and surprising that BNP measurements and cardiac necrosis markers such as troponin measurements would provide independent prognostic information in acute coronary syndromes (ACS) and so when combined, would provide improved ability to stratify risk in patients in comparison to either BNP or cardiac troponin alone. Applicants assert that the prior art would lead the skilled artisan to erroneously believe that BNP, to the extent it would provide any information at all, would provide similar information to cardiac necrosis markers such as troponin, and not independent information. Such argument however is not persuasive as Richards et al. disclose in Table 1 on page 115 that troponin T was also measured as part of the clinical features of the patients in the study. While troponin T is distinct from troponin I taught in Antman et al., and Richards et al. do not teach troponin T as a prognostic marker of likelihood of death, the disclosure by Richards et al. of measuring troponin T as well as BNP, and the determination that BNP is a powerful predictor of

death, nevertheless suggest the opposite of Applicants' assertion that the prior art would lead the skilled artisan to erroneously believe that BNP would provide similar information to cardiac necrosis markers such as troponin. That is, there is no indication in any of the cited references that BNP would provide similar information to troponin (either I or T). To the contrary, the teachings of all three references suggest that different markers provide additional information, with Jackowski teaching that different markers are elevated and peak at different times and thus one marker may be insufficient, and Antman et al. teaching that elevated levels of troponin I correlates to increased risk of death even 0 to 6 hours after onset of chest pain, and more strongly correlates at 6 to 24 hours, and Richards et al. teaching a different time frame in measuring BNP, that is, 24 to 96 hours after onset of symptoms, for predicting death.

Applicants further argue on page 11 that, additionally, it was unexpected that BNP measurements and cardiac troponin measurements would provide independent prognostic information across the entire spectrum of ACS conditions, and not only in acute myocardial infarction. Applicants argues that the importance of Applicants' contribution in this regard has been widely recognized, acknowledged, and adopted in the art, and that the unexpected properties of the claimed invention, and the secondary considerations represented by the widespread approval and adoption of the claimed invention in the art, rebut any prima facie case of obviousness. These arguments however do not rebut the obviousness rejection because these argument are not directed to the limitations claimed by Applicants that are rejected by Examiner. That is, Applicants' claims do not recite measuring BNP and cardiac troponin levels to provide

prognostic information across the entire spectrum of ACS conditions, nor do Applicants claims exclude measuring BNP and cardiac troponin levels in patients with acute myocardial infarction, and thus Applicants' assertion that it was unexpected that BNP measurements and cardiac troponin measurements would provide independent prognostic information across the entire spectrum of ACS conditions, and not only in acute myocardial infarction, does not rebut Examiner obviousness rejection.

Applicants further assert at the bottom of page 11 that shortly after the filing date of the present application, the data and conclusions contained in the present application were published in the *New England Journal of Medicine*, (NEJM), perhaps the preeminent medical journal in the world. Applicants emphasize that as taught in the present specification and confirmed through subsequent publication in the NEJM, the present inventors discovered that BNP measurements and cardiac troponin measurements provide independent prognostic information in ACS patients. Applicants also emphasize that the NEJM's editors also published an Editorial in the same NEJM issue, emphasizing the importance of the discovery to its readers. The editorial as cited by Applicants states that use of electrocardiographic findings, and the levels of traditional serum markers of myocyte necrosis, such as creatine kinase MB fraction and troponin I, is only partially successful in risk stratification, and that elevated troponin level confers an increased short-term risk of death. The editorial also states that as compared with data from cohort studies, troponin level has less prognostic value, and also that measurement of three markers of myocyte necrosis—troponin I, creatine kinase MB, and myoglobin—significantly increased physicians' ability to detect acute

coronary syndromes, as compared with the use of each marker alone. The editorial further states that the issue of the Journal contains two articles—one by de Lemos et al. and one by Bayes-Genis et al.—on important new markers for use in risk stratification for acute coronary syndromes, and that it is found that a single measurement of BNP obtained a median of 40 hours after the onset of ischemic symptoms predicted the risk of death, and that the relation between the long-term risk of death and the BNP level was independent of electrocardiographic changes, troponin I levels, renal function, and the presence or absence of clinical evidence of congestive heart failure.

While the publication in NEJM and the editorial provides evidence of the importance of, among other things, BNP as an independent predictor of long-term risk of death, as well as the fact that elevated troponin level [presumably troponin I, rather than T or C, but it is noted that this is not clear] confers an increased short-term risk of death, Applicants have not shown that this is unexpected. That is, Applicants have not provided evidence as to what was expected, in contrast to Applicants' findings, thus showing unexpected findings. First, it is noted that the discovery that troponin I is an independent predictor of death is disclosed by the Antman et al. prior art reference, and the discovery that BNP is an independent predictor of death is disclosed by Richards et al. Secondly, Applicants' evidence does not support unexpected findings. That is, Applicants have not indicated nor provided evidence supporting that it is expected that BNP and troponin I would provide the same prognosis in terms of the short-term or long-term risk of death, and that discovering that BNP is a predictor of long-term risk of death, while troponin I confers only an increased short-term risk of death is an

unexpected result. Examiner has considered Applicants' response in its entirety as well as the affidavit of Dr. Paradis, and finds no substantial support that such findings are unexpected. More specifically, Applicants asserts on page 13, which refer to Dr. Paradis's affidavit, and Dr. Paradis's affidavit on paragraph 5 also assert that one reason for the surprising nature and importance of Applicants' finding may be gleaned from the prior art disclosure of Hassan and co-workers that BNP was significantly increased in the case of cardiac necrosis but did not increase due to cardiac ischemia, which would lead the skilled artisan to conclude that BNP, like cardiac troponin, would not be independent markers. However, this does not support that it is expected that BNP and troponin I would provide the same prognosis in terms of the short-term or long-term risk of death, nor the risk of death during any length of duration, nor that discovering that BNP is a predictor of long-term risk of death, while troponin I confers only an increased short-term risk of death, is an unexpected result. Also, Applicants' response on page 13, and Dr. Paradis's declaration on paragraph 10, assert that Sabatine et al. report on the use of BNP, cardiac troponin I, and an inflammatory marker (C-reactive protein) in a multimarker strategy for risk stratification in non-ST elevation ACS, the authors stating that a multimarker strategy that categorizes patients based on the number of elevated biomarkers at presentation allows risk stratification over a broad range of short- and long-term major cardiac events. Applicants state that these results are of a significant practical advantage, as the combined markers provide an improved prognosis of ACS patients. However the disclosure by Sabatine et al. (2002) is not mentioned by Applicants to be specifically related to *prognosis of death*, and also do not

provide evidence that it is unexpected that BNP is a predictor of long-term risk of death while troponin I confers only an increased short-term risk of death. Submitted evidence showing what was expected in contrast to Applicants' findings regarding the long-term and short-term risk of death would be appropriately considered. Such evidence would be vital in establishing unexpected results that BNP and troponin I each provide a different or additional prognosis regarding long-term or short-term risk of death, particularly in light of the fact that Antman et al. disclose that mortality was calculated at 42 days (see fig. 2), and Richards et al. disclose that clinical events including death were recorded over a mean follow up period of 14 months [i.e., a much longer period], (see page 115, left column second full paragraph.)

As to the disclosure in the Journal or editorial that using three different markers significantly increased a physicians' ability to detect acute coronary syndromes, as compared with the use of each marker alone, such a suggestion has already been made by Jackowski (see for example col. 7, lines 47-51, and col. 8, lines 16-38.) It is also noted that the claims are directed to predicting death, not detecting acute coronary syndromes.

Applicants also point out at the bottom of page 12 that within less than one year of the publication of this data from the present application in NEJM, researchers published a similar article concerning the biosynthetically related polypeptide NT-proBNP, demonstrating that NT-proBNP and cardiac troponin measurements also provide independent prognostic information in ACS, and stating that BNP and NT-proBNP are remarkably similar in this regard. This evidence however does not rebut a

the prima facie case of obviousness for the same reasons set forth above. The evidence also does not rebut the obviousness rejection additionally because it is not relevant to the rejection which is based on teachings of BNP, rather than proBNP or NT-proBNP, where the claims list BNP as one of the markers as an alternative to proBNP and NT-proBNP.

Applicants also state at the bottom of page 13 that according to Dr. Paradis, this practical advantage has been widely recognized, acknowledged, and adopted in the art, as demonstrated by report by Silver et al. (2004) prepared by an expert panel gathered by selecting clinicians and scientists with expertise with the natriuretic peptide system. To show the practical advantage of combined measurements of BNP and cardiac troponin, Applicants cited the report's statement that when used together in a combined strategy, BNP and cardiac troponin provide a more effective tool for identifying patients at increased risk for clinically important cardiac events related to HF [presumably heart failure] and acute coronary syndrome, and that multimarker panels that include BNP, troponin, and C-reactive protein are now available and each of these markers provides unique and independent information with regard to patient outcomes. Applicants' citation of the report however does not indicate that cardiac events includes death, and thus does not provide direct evidence related to Applicants' claims, which are directed to predicting likelihood of death.

Applicants also argue that the present invention is applicable not just in acute myocardial infarction, but also provides powerful risk-stratification across the entire spectrum of acute coronary syndromes, including for example unstable angina.

Applicants assert that Richards et al., in contrast, evaluated a subject population that featured only individuals having ST-elevation myocardial infarction, and is silent on the use of BNP measurements in ACS conditions other than acute myocardial infarctions.

Applicants further state that while the cited art focuses only on this ST-elevation myocardial infarction population, the present invention reports for the first time that BNP is an independent prognostic marker, relative to cardiac troponins, across the entire spectrum of ACS conditions including conditions such as myocardial infarction without ST-segment elevation and unstable angina. Applicants' argument on page 14, refers to Dr. Paradis' affidavit in paragraphs 7 and 8 of his declaration, which state that this feature of the present invention was again of such significance that its publication in the de Lemos et al. NEJM article warranted special mention in the accompanying editorial. Applicants further maintain that the claimed invention can provide prognostic information across the entire spectrum of acute coronary syndromes was unexpected because the scientific literature at the time indicated that BNP measurements would not be applicable outside of the context of acute myocardial infarction. Applicants point out that acute myocardial infarction refers to necrosis of the myocardium, and other ACS conditions, such as unstable angina, are diseases of ischemia, but not diseases of necrosis. Applicants state that given such a teaching that BNP would not be increased outside of the context of acute myocardial infarction, Dr. Paradis concludes, in the declaration on paragraph 9, that one of ordinary skill was surprised to learn that BNP is an independent prognostic marker, relative to cardiac troponins, even in ACS conditions such as unstable angina.

As indicated earlier, and as reiterated here, these statements do not rebut the obviousness rejection because these argument are not directed to the limitations claimed by Applicants that are rejected by Examiner. That is, Applicants' claims do not recite measuring BNP and cardiac troponin levels to provide prognostic information across the entire spectrum of ACS conditions, nor do Applicants claims exclude measuring BNP and cardiac troponin levels in patients with acute myocardial infarction, and thus Applicants' assertion that it was unexpected that BNP measurements and cardiac troponin measurements would provide independent prognostic information across the entire spectrum of ACS conditions, and not only in acute myocardial infarction, does not rebut Examiner obviousness rejection.

The affidavit of Dr. Paradis is acknowledged and has been considered by Examiner, but are not persuasive. The points made in the affidavit have also been incorporated into Applicants' response, and thus the points made in the affidavit have been addressed as indicated above. However, the response to Dr. Paradis's affidavit will be summarized as follows. Paragraph 5 of the affidavit assert that the surprising nature of the discovery that BNP as a prognostic marker is independent of what are considered "traditional" markers of cardiac necrosis such as cardiac troponins comes from a review of the scientific literature. The affidavit cites the work of Hassan and co-workers, who concluded that while BNP was significantly increased in the case of cardiac necrosis, BNP did not increase due to cardiac ischemia. The affidavit asserts that this would lead the skilled artisan to believe that BNP, like cardiac troponins, increase presumably because the amount of myocardial necrosis increases, and thus

the skilled artisan would conclude that BNP would provide similar information to other necrosis markers such as troponin, which thus show that the evidence provided in the present invention that this is not the case, then was quite surprising. As indicated earlier, this does not support that it is expected that BNP and troponin I would provide the *same* prognosis for *risk of death*, short-term, long-term or for any duration of time.

The affidavit also makes a point in paragraph 6 that confirmation for the conclusion of the surprising nature of the discovery is provided by an editorial by Rabbani in an NEJM publication. The editorial as cited by Applicants states that a single measurement of BNP predicted the risk of death in patients who had myocardial infarction or unstable angina, and that the long-term risk of death and the BNP level was independent of electrocardiographic changes, troponin I levels, renal function and evidence of congestive heart failure, and that even in patients who had unstable angina and no evidence of myocyte necrosis on the basis of the absence of an elevation in troponin I levels, an elevation in BNP levels portended a worse prognosis. However, the citation in the editorial does not show that these discoveries in measuring BNP and troponin were unexpected, particularly in light of the fact that the prior art suggests that cardiac markers are elevated and peak at different times.

The affidavit also makes a point in paragraphs 8 and 9 that the Hassan et al. publication would lead the skilled artisan to believe that BNP, like cardiac troponins, increases presumably because the amount of myocardial necrosis increases and thus the skilled artisan would not have been led to believe that BNP would be a prognostic marker across the entire spectrum of acute coronary syndromes, and not just

myocardial infarction. As indicated earlier, these statements however do not rebut the obviousness rejection because these argument are not directed to the limitations claimed by Applicants that are rejected by Examiner. That is, Applicants' claims do not recite measuring BNP and cardiac troponin levels to provide prognostic information across the entire spectrum of ACS conditions, nor do Applicants claims exclude measuring BNP and cardiac troponin levels in patients with acute myocardial infarction, and thus Applicants' assertion that it was unexpected that BNP measurements and cardiac troponin measurements would provide independent prognostic information across the entire spectrum of ACS conditions, and not only in acute myocardial infarction,does not rebut Examiner obviousness rejection.

As to paragraph 10, the declaration asserts that the Sabatine et al. (2002) reference reports on the use of BNP, cardiac troponin I, and an inflammatory marker (C-reactive protein) in a multimarker strategy for risk stratification in non-ST elevation ACS, with the authors stating that a multimarker strategy that categorizes patients based on the number of elevated biomarkers at presentation allows risk stratification over a broad range of short- and long-term major cardiac events. However the disclosure by Sabatine et al. is not mentioned by Applicants to be specifically related to *prognosis of death*, and also do not provide evidence that it is unexpected that BNP is a predictor of long-term risk of death while troponin I confers only a limited prognosis of an increased death in the short-term. Such evidence would be vital in establishing unexpected results that BNP and troponin I each provide a different or additional prognosis regarding long-term or short-term risk of death, particularly in light of the fact that Antman et al. disclose that

mortality was calculated at 42 days (see fig. 2), and Richards et al. disclose that clinical events including death were recorded over a mean follow up period of 14 months [i.e., a much longer period], (see page 115, left column second full paragraph.)

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ann Y. Lam whose telephone number is 571-272-0822. The examiner can normally be reached on Mon.-Fri. 10-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ANN YEN LAM
PATENT EXAMINER